

THE EFFECT OF BARIATRIC SURGERY ON BREAST CANCER INCIDENCE AND CHARACTERISTICS: A COMPREHENSIVE SYSTEMATIC REVIEW

^{1*}Rokhim Suryadi, ²Bambang Supriyo, ³Yosie Yulanda Putra, ⁴Ahsan Auliya, ⁵M. Yudhi Hardiyansah

^{1*}*Faculty of Medicine, Trisakti University, Jakarta Special Region, Indonesia*

²*General Surgery Consultant, Department of Surgery, Hawari Essa Hospital, Tegal, Central Java, Indonesia*

³*H. Bakri Sungai Penuh Regional General Hospital, Jambi, Indonesia*

⁴*Pertamedika Baiturrahim General Hospital, Jambi, Indonesia*

⁵*Faculty of Medicine, Malahayati University, Jakarta Special Region, Indonesia*

Correspondence Author:

dr.rokhimsuryadi@gmail.com

ABSTRACT

Background: Obesity elevates estrogen levels and pro-inflammatory cytokines, increasing breast cancer risk via macrophage migration to breast tissue and stimulating epithelial proliferation. Observational studies suggest that intentional weight loss, such as through bariatric surgery, can mitigate this risk. This study aims to conduct a comprehensive systematic review, focusing on the impact of bariatric surgery on breast cancer incidence and characteristics using recent literature.

Methods: The systematic review followed PRISMA 2020 standards and examined full-text English literature published between 2014 and 2024. This review excluded editorials, review papers from the same journal, and submissions without a DOI. Literature was sourced from online platforms such as PubMed, SagePub, and SpringerLink.

Result: A total of 1,011 articles were retrieved from online databases (PubMed, SagePub, and SpringerLink). After three rounds of screening, five articles directly relevant to the systematic review were selected for full-text reading and analysis.

Conclusion: Bariatric surgery decreases overall cancer risk in women, especially for breast cancer, by lowering estrogen levels and altering tumor biology. It also improves glucose homeostasis and reduces insulin resistance, both linked to higher cancer risk.

Keyword: Breast cancer, cancer incidence, bariatric surgery

INTRODUCTION

Obesity is a complex chronic condition characterized by an excessive accumulation of body fat, which poses significant health risks, including an increased susceptibility to various types of cancer. Among these cancers, breast cancer stands out as a prominent concern, particularly among women in the USA and Canada. It ranks as the most frequently diagnosed cancer in this demographic and is the second leading cause of cancer-related death, emphasizing the urgent need to comprehend its underlying factors.¹

Large-scale epidemiological studies and systematic reviews has consistently highlighted the strong association between obesity and breast cancer risk. Notably, this correlation appears to be particularly pronounced in post-menopausal women, where increasing body mass index (BMI) and adiposity exhibit a linear relationship with breast cancer incidence. Higher estrogen levels and pro-inflammatory cytokines contribute to increased risk of breast cancer by promoting macrophage migration to breast tissue and stimulating breast epithelial proliferation. Observational studies indicate that intentional weight loss can reduce the risk of breast cancer. Significant weight loss of more than 10% over a six-month period is associated with favorable changes in serum markers, including sex hormone-binding globulin, insulin-like growth factor, C-reactive protein, estradiol, interleukin-6, and tumor necrosis factor alpha, which are linked to breast cancer risk modulation.²

The implications of these findings are profound, emphasizing the necessity of comprehensive strategies aimed at preventing and managing obesity to mitigate breast cancer risk. Public health initiatives focused on promoting healthy lifestyle behaviors, such as regular physical activity and balanced nutrition, are crucial in this regard. Furthermore, continued research into the mechanisms underlying the obesity-breast cancer link is essential for the development of targeted interventions and treatments. By addressing obesity as a modifiable risk factor, there is potential to reduce the burden of breast cancer and improve overall public health outcomes.³

Lifestyle-based behavioral and pharmacological interventions are the primary approaches for preventing and managing obesity, but their success is limited. Bariatric surgery has emerged as the most effective method for achieving weight loss in obese patients, both in the short and long term, surpassing the effectiveness of traditional dieting methods. Weight loss following bariatric surgery offers significant health advantages, such as the resolution of type 2 diabetes in the majority of treated patients and reduced overall mortality, primarily due to a decrease in major cardiovascular events.^{3,4}

Many studies investigating the relationship between bariatric surgery and cancer primarily concentrate on weight loss and various types of cancer rather than specific characteristics of breast cancer. Consequently, the precise impact of bariatric surgery on the occurrence and outcomes of breast cancer is frequently not thoroughly examined or obscured due to insufficient reported data. While there is a clear epidemiological connection between breast cancer and obesity, the extent of the benefit of surgical weight loss on breast cancer incidence and outcomes remains uncertain.⁴ The objective of this study is to conduct an extensive systematic review focusing on the effect of bariatric surgery on the incidence and characteristics of breast cancer based on literature published within the past decade.

METHODS

Protocol

The author carefully followed the rules laid out in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. This was done to make sure the study met all its standards. The selection of this methodological approach was specifically aimed at ensuring the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review examined the effect of bariatric surgery on the incidence and characteristics of breast cancer based on literature published within the past decade. This study meticulously analyzed data on literatures to provide insights and enhance patient treatment strategies. The primary objective of this paper is to highlight the collective significance of the identified key points.

Inclusion criteria for this study entail: 1) Papers must be in English, and 2) Papers must have been published between 2014 and 2024. Exclusion criteria comprise: 1) Editorials; 2) Submissions without a DOI; 3) Previously published review articles; and 4) Duplicate entries in journals.

Search Strategy

The keywords used for this research are “breast cancer”, “cancer incidence”, and “bariatric surgery”. The Boolean MeSH keywords inputted on databases for this research are: (*"breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields] AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields]*)

OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms] OR "incidences"[All Fields] OR "incident"[All Fields] OR "incidents"[All Fields])) AND ("bariatric surgery"[MeSH Terms] OR ("bariatric"[All Fields] AND "surgery"[All Fields]) OR "bariatric surgery"[All Fields])) AND (y_10[Filter])

Data retrieval

The authors assessed the studies by reviewing their abstracts and titles to determine their eligibility, selecting relevant ones based on their adherence to the inclusion criteria, which aligned with the article's objectives. A consistent trend observed across multiple studies led to a conclusive result. The chosen submissions had to meet the eligibility criteria of being in English and a full-text.

This systematic review exclusively incorporated literature that met all predefined inclusion criteria and directly pertained to the investigated topic. Studies failing to meet these criteria were systematically excluded, and their findings were not considered. Subsequent analysis examined various details uncovered during the research process, including titles, authors, publication dates, locations, study methodologies, and parameters.

Quality Assessment and Data Synthesis

Each author independently evaluated the research presented in the title and abstract of the publication to determine which ones merited further exploration. The subsequent stage involved assessing all articles that met the predefined criteria for inclusion in the review. Decisions on including articles in the review were based on the findings uncovered during this evaluation process. This criterion aimed to streamline the paper selection process for further assessment, facilitating a comprehensive discussion of previous investigations and the factors that made them suitable for inclusion in the review.

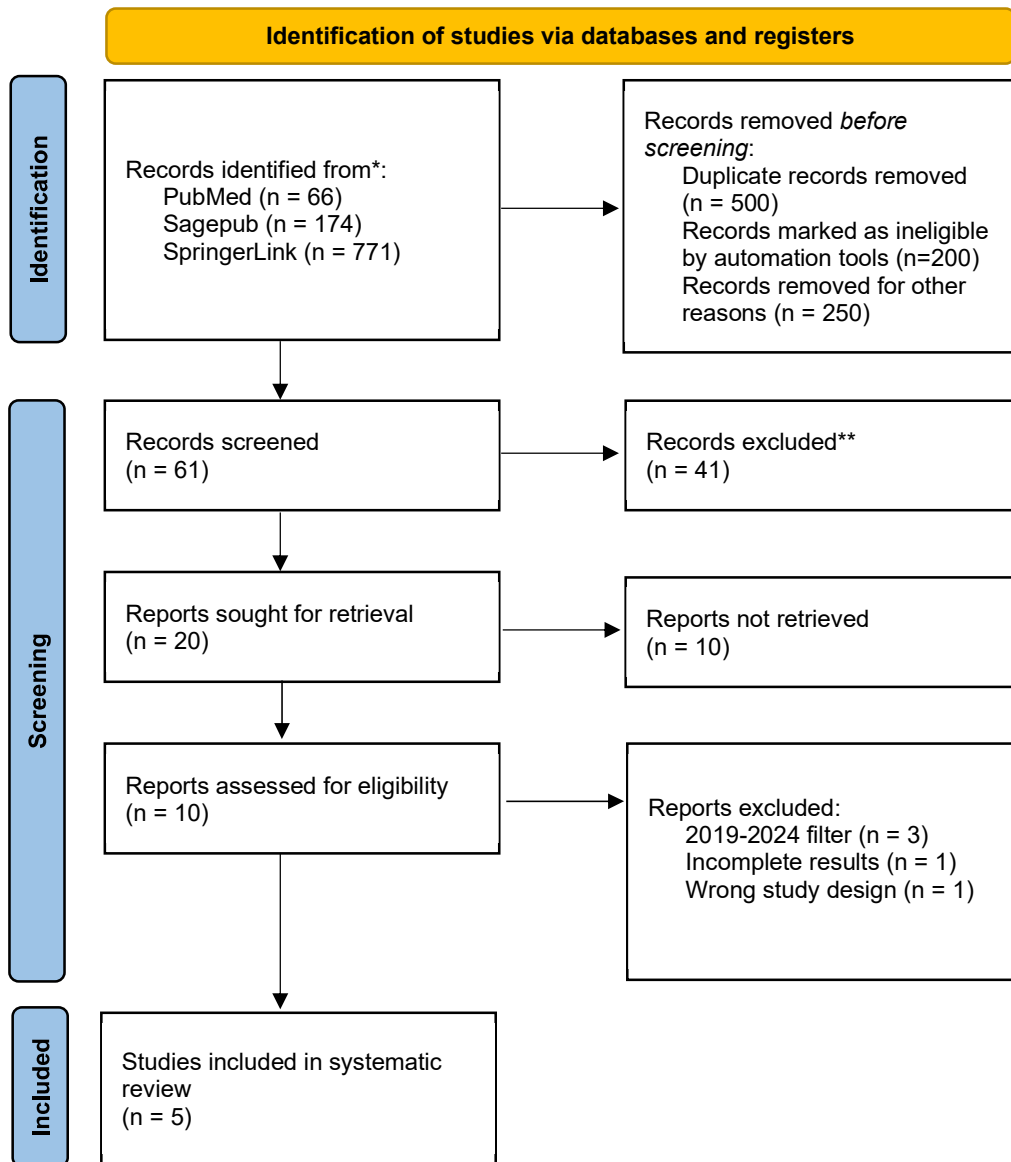


Figure 1. Article search flowchart

RESULT

The initial number of articles retrieved from online databases (PubMed, SagePub, and SpringerLink) is 1,011 articles. After conducting three levels of screening, five articles that directly relate to the current systematic review have been chosen for further assessment through full-text reading and analysis. Table 1 presents the selected literature included in this analysis.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Anveden, et al. ⁵ (2017)	Swedia	Prospective study	1420 bariatric surgery patient and 1447 control	The prospective Swedish Obese Subjects (SOS) study aimed to evaluate outcomes following bariatric surgery, involving 1420 women from the SOS cohort who underwent the procedure and 1447 matched controls

				<p>receiving conventional obesity treatment. Participants, aged 37 to 60 years with a BMI ≥ 38 kg/m², were tracked for a median follow-up period of 18.1 years. Cancer incidence data were gathered from the Swedish National Cancer Registry, with the study registered on ClinicalTrials.gov under NCT01479452. Results indicated that bariatric surgery correlated with a reduced risk of overall cancer (HR=0.71; 95% CI 0.59–0.85; p<0.001). Notably, around half of the observed cancers were female-specific, with the surgery group exhibiting a lower incidence compared to controls (HR=0.68; 95% CI 0.52–0.88; p=0.004). Further analysis revealed that the benefits of surgical treatment concerning female-specific cancer were notably associated with baseline serum insulin levels, showing a greater relative benefit in patients with medium or high insulin levels. Additionally, separate analyses indicated a reduced risk of endometrial cancer following bariatric surgery (HR=0.56; 95% CI 0.35–0.89; p=0.014).</p>
<p>Schauer, et al.⁶ (2019)</p>	<p>Multicenter</p>	<p>Retrospective cohort study</p>	<p>22,198 bariatric surgery patients and 66,427 controls</p>	<p>The study included 22,198 subjects who underwent bariatric surgery and 66,427 nonsurgical subjects matched on various factors. Multivariable Cox proportional-hazards models were utilized to examine incident cancer up to 10 years post-bariatric surgery compared to matched nonsurgical patients. Results revealed that after a</p>

				<p>mean follow-up of 3.5 years, 2543 incident cancers were identified. Patients who underwent bariatric surgery exhibited a 33% lower hazard of developing any cancer during follow-up compared to matched patients with severe obesity who did not undergo surgery. This risk reduction was even more pronounced for obesity-associated cancers. Specifically, the risk of postmenopausal breast cancer, colon cancer, endometrial cancer, and pancreatic cancer was significantly lower among those who had undergone bariatric surgery compared to matched nonsurgical patients.</p>
<p>Hassinger, et al.⁷ (2019)</p>	<p>Virginia, USA</p>	<p>Retrospective study</p>	<p>4860 patients</p>	<p>The study examined female patients who underwent weight loss surgery at a single institution from 1985 to 2015. Propensity score matching was used to compare patients based on BMI, comorbidities, demographics, and insurance status. Results showed that out of the 4860 patients included, 2430 were in both groups, with a median follow-up time of 5.7 years from the date of surgery or morbid obesity diagnosis. No significant differences in age or comorbidities were observed except for gastroesophageal reflux disease. Notably, 17 (0.7%) patients in the surgery group were subsequently diagnosed with breast cancer compared to 32 (1.3%) in the nonsurgery group (p = 0.03). Furthermore, the nonsurgery group had a higher incidence of ER-positive tumors</p>

				(4 (36.4%) vs. 22 (71.0%); p = 0.04).
Feigelson, et al.⁸ (2020)	Multicenter	Retrospective cohort study	301 premenopausal and 399 postmenopausal breast cancer patients	The study focused on severely obese female patients enrolled in an integrated health care system from 2005 to 2012, with follow-up until 2014. The analysis included 301 premenopausal and 399 postmenopausal breast cancer cases. Results revealed a reduced risk of both premenopausal (HR = 0.72, 95% CI, 0.54–0.94) and postmenopausal (HR = 0.55, 95% CI, 0.42–0.72) breast cancer following bariatric surgery. Notably, the effect was more significant in ER-negative cases among premenopausal women (HR = 0.36, 95% CI, 0.16–0.79) and in ER-positive cases among postmenopausal women (HR = 0.52, 95% CI, 0.39–0.70).
Heshmati, et al.⁹ (2019)	Multicenter	Retrospective cohort study	42 subjects diagnosed with breast cancer after bariatric surgery and 84 subjects with breast cancer who did not undergo bariatric surgery	Results showed that women with breast cancer after bariatric surgery presented at earlier stages compared to non-operated, obese controls. Additionally, fewer tumors exhibited human epidermal growth factor receptor 2 overexpression (HER2+) in the bariatric surgery group, with Roux-en-Y gastric bypass patients having no HER2+ cancers. Multivariate analysis confirmed the association between bariatric surgery and reduced HER2+ breast cancers. Furthermore, at a mean 5-year follow-up, bariatric surgery was linked to trends toward decreased cancer-specific and all-cause mortality.

Anveden, et al.⁵ (2017) showed that there was an association between bariatric surgery and a decreased risk of female-specific cancer, particularly among women with hyperinsulinemia at baseline. Further analysis revealed that the benefits of surgical treatment concerning female-specific cancer were notably associated with baseline serum insulin levels, showing a greater relative benefit in patients with medium or high insulin levels. Additionally, separate analyses indicated a reduced risk of endometrial cancer following bariatric surgery.

Schauer, et al.⁶ (2019) demonstrated that bariatric surgery was associated with a reduced risk of incident cancer, particularly obesity-associated cancers like postmenopausal breast cancer, endometrial cancer, and colon cancer. However, further research is needed to elucidate the specific mechanisms through which bariatric surgery lowers cancer risk.

Hassinger, et al.⁷ (2019) concluded that female patients who underwent bariatric surgery were less frequently diagnosed with any breast cancer and ER-positive breast cancer compared to a propensity-matched cohort, suggesting a potential oncologic benefit associated with weight loss surgery.

Feigelson, et al.⁸ (2020) found that bariatric surgery was linked to a decreased risk of breast cancer in severely obese women. These results hold importance in public health due to the ongoing increase in obesity rates and the limited number of modifiable risk factors for breast cancer, particularly among premenopausal women.

Heshmati, et al.⁹ (2019) suggested that bariatric surgery may influence breast cancer characteristics and tumor biology, particularly in reducing human epidermal growth factor receptor 2 overexpression (HER2+) in breast cancers.

DISCUSSION

This systematic review investigated the impact of bariatric surgery on breast cancer incidence and characteristics. The established link between obesity and cancer is further supported by this review, which confirms the previously reported protective effect of bariatric surgery on overall cancer risk in women. Additionally, the study reveals a significant association between bariatric surgery and a reduced risk of female-specific cancers, including breast, endometrial, ovarian, and other gynecological cancers. Notably, these female-specific cancers accounted for about half of the observed cancer events in the cohort and are prevalent among the obese population. For instance, up to 40.8% of endometrial cancer cases in the UK have been attributed to obesity.⁵

This diversity in cancer reduction rates among obesity-related cancers is unsurprising, given the numerous mechanisms through which obesity elevates cancer risk. The most substantial reductions in cancer risk were observed for postmenopausal breast and endometrial cancers, which are highly sensitive to estrogen levels and respond quickly to changes. In women, especially post-menopause when adipose tissue becomes a significant source of estrogen synthesis, higher levels of body fat correlate strongly with increased circulating estrogen. This heightened estrogen production has been linked to breast tumors with estrogen levels up to ten times higher than those found in circulation. Consequently, both body mass index (BMI) and weight gain between ages 20 and 50 are considered significant risk factors for breast cancer development.^{6,7}

Proposed mechanisms for breast cancer risk reduction after bariatric surgery involve a decrease in the conversion of estradiol to estrogen due to decreased adipose tissue. Indeed, circulating estrogen levels in postmenopausal females show a direct correlation with weight, and adjusting for serum estrogen concentrations nearly eliminates the association between BMI and postmenopausal breast cancer. Additionally, another study suggested that bariatric surgery may influence breast cancer characteristics and tumor biology, particularly in reducing human epidermal growth factor receptor 2 overexpression (HER2+) in breast cancers.^{6,9}

Apart from estrogen levels, cancer risk is heightened in patients with metabolic syndrome due to factors such as insulin and inflammation. Insulin is believed to promote cancer development due to its role as a growth factor with metabolic and mitogenic effects, and hyperinsulinemia is considered a contributing factor to the obesity-cancer connection. Moreover, insulin is associated with endocrine risk factors for cancer, such as insulin-like growth factor 1, sex steroids, and adipokines, and studies have shown that insulin levels decrease following bariatric surgery.⁹

Bariatric surgery offers additional benefits, potentially impacting cancer incidence, through improved glucose homeostasis and decreased insulin resistance. Feigelson, et al.⁸ (2020) found that bariatric surgery was linked to a decreased risk of breast cancer in severely obese women, both post menopausal and premenopausal. It's increasingly understood that premenopausal breast cancer may have different causes than postmenopausal cases, with inflammation or insulin pathways potentially playing a more significant role in premenopausal women. Additionally, bariatric surgery is linked to alterations in the gut microbiome composition, resembling that of leaner individuals post-operation. Changes in gut microbial diversity have been linked to breast cancer, suggesting that modifications in the gut microbiota may contribute to decreased cancer risk following bariatric surgery.⁸

CONCLUSION

Bariatric surgery reduces the overall cancer risk in women, particularly targeting female-specific cancers such as breast cancer. This mechanism is achieved by decreasing estrogen levels and modifying tumor biology in cancer development. Bariatric surgery's mechanisms for reducing breast cancer risk involve decreasing estrogen levels and altering tumor biology. Furthermore, the surgery improves glucose homeostasis and reduces insulin resistance, both of which are actively associated with increased cancer risk.

REFERENCES

- [1] Doumouras AG, Lovrics O, Paterson JM, Sutradhar R, Paszat L, Sivapathasundaram B, et al. Bariatric Surgery and Breast Cancer Incidence: a Population-Based, Matched Cohort Study. *OBES SURG.* 2022 Apr 1;32(4):1261–9. Available from: <https://doi.org/10.1007/s11695-022-05946-9>
- [2] Winder AA, Kularatna M, MacCormick AD. Does Bariatric Surgery Affect the Incidence of Breast Cancer Development? A Systematic Review. *OBES SURG.* 2017 Nov 1;27(11):3014–20. Available from: <https://doi.org/10.1007/s11695-017-2901-5>
- [3] Zhang K, Luo Y, Dai H, Deng Z. Effects of Bariatric Surgery on Cancer Risk: Evidence from Meta-analysis. *OBES SURG.* 2020 Apr;30(4):1265–72. Available from: <http://link.springer.com/10.1007/s11695-019-04368-4>
- [4] Lovrics O, Butt J, Lee Y, Lovrics P, Boudreau V, Anvari M, et al. The effect of bariatric surgery on breast cancer incidence and characteristics: A meta-analysis and systematic review. *The American Journal of Surgery.* 2021 Oct 1;222(4):715–22. Available from: <https://www.sciencedirect.com/science/article/pii/S0002961021001513>
- [5] Anveden Å, Taube M, Peltonen M, Jacobson P, Andersson-Assarsson JC, Sjöholm K, et al. Long-term incidence of female-specific cancer after bariatric surgery or usual care in the Swedish Obese Subjects Study. *Gynecologic Oncology.* 2017 May 1;145(2):224–9. Available from: <https://www.sciencedirect.com/science/article/pii/S0090825817301580>
- [6] Schauer DP, Feigelson HS, Koebnick C, Caan B, Weinmann S, Leonard AC, et al. Bariatric Surgery and the Risk of Cancer in a Large Multisite Cohort. *Annals of Surgery.* 2019 Jan;269(1):95. Available from: https://journals.lww.com/annalsofsurgery/abstract/2019/01000/bariatric_surgery_and_the_risk_of_cancer_in_a_21.aspx
- [7] Hassinger TE, Mehaffey JH, Hawkins RB, Schirmer BD, Hallowell PT, Schroen AT, et al. Overall and Estrogen Receptor-Positive Breast Cancer Incidences Are Decreased Following Bariatric Surgery. *OBES SURG.* 2019 Mar 1;29(3):776–81. Available from: <https://doi.org/10.1007/s11695-018-3598-9>
- [8] Feigelson HS, Caan B, Weinmann S, Leonard AC, Powers JD, Yenumula PR, et al. Bariatric Surgery is Associated With Reduced Risk of Breast Cancer in Both Premenopausal and Postmenopausal Women. *Annals of Surgery.* 2020 Dec;272(6):1053. Available from: https://journals.lww.com/annalsofsurgery/abstract/2020/12000/bariatric_surgery_is_associated_with_reduced_risk.29.aspx
- [9] Heshmati K, Harris DA, Rosner B, Pranckevicius E, Ardestani A, Cho N, et al. Association of Bariatric Surgery Status with Reduced HER2+ Breast Cancers: a Retrospective Cohort Study. *OBES SURG.* 2019 Apr 1;29(4):1092–8. Available from: <https://doi.org/10.1007/s11695-018-03701-7>